doesn't make it unimportant. It makes it perhaps more important because we need to understand how to detect these kinds of changes if they occur in humans.

So, number two, confirming the criticality and validating the problem. In the 1980s and 1990s, we worked with a variety of different cardiovascular agents that at high doses caused hypotension, reflex tachycardia, myocardial necrosis that Dr. Holt will talk about, and also vascular disease. And we were quite comfortable with that for reasons that, on reflection, may not seem realistic, but quite comfortable with that and thinking that if we did not induce hypotension and reflex tachycardia in humans then we would not induce vascular disease. This is clearly true for myocardial toxicity, but unproven for vascular toxicity.

So, we now have a series of new drugs that we're working with in Pharma and within the agency that cause vascular disease but they do not cause changes in blood pressure and heart rate.

Once again, lesions that we see in humans are not observed in routine toxicity studies in normal animals. The common drug-induced lesions that we do see in animals are not known to occur in humans and have unknown relevance. There are, as I said, five marketed products on the market that cause these lesions.

But lastly and importantly, even though they are unknown to occur, there are, however, no methods for detecting drug-induced vascular injury as I've described in animals or humans prospectively.

So, drug-induced vascular injury in animals does warrant an investment of resources to define early and predictive biomarkers of injury and possibly mechanism. The EWG then recommends proceeding to organize the funds and the process necessary to develop and validate specific markers.

The next item we took in our charge was then to develop a list of prospective biomarkers. Although the pathogenesis of vascular injury in animals is not clear, it is clear to the pathologists that have looked at these changes that the initial events appear to occur by perturbations of endothelial integrity. And secondly, it's clear to many of us who've worked in the field that the changes that we see are not a result of direct toxic action of compounds on the endothelium, but more importantly probably an effect of altered function, changes in blood flow, changes in fluid dynamics, changes in shear stress, and lastly, changes in hoop stress within the vascular wall, and that these factors are probably more important than direct toxicity.

Endothelial compromise, then, appears to play

an important early role in the development of this syndrome, and therefore our biomarkers might be targeted to endothelial compromise.

So, the charge then is to develop noninvasive methods to monitor endothelial and vascular smooth muscle cell damage in a variety of preclinical animal species.

Equally important, in the inflammatory process that ensues in this disease, there are many other inflammatory cells, neutrophils and platelets, involved in the process, and we're also thinking that these platelets and neutrophils, taken ex vivo, might be able to tell us something with regard to new biomarkers, proteins that might be upregulated in these cells that we can look at ex vivo in animals and potentially in humans.

And lastly and importantly and probably most difficult, once new markers are identified, then validating the new marker both in preclinical species and transferring that to practice in phase 1.

The markers that we are targeting initially as of our initial meeting and as a result of several e-mail discussions in the interim, would be vascular endothelial growth factor and its soluble receptor, sF1t-1, von Willebrand factor, thrombomodulin, CD62E, E-selectin.

Circulating endothelial cells. There have been a few publications recently from Europe looking at

circulating endothelial cells following angioplasty. I can tell you just briefly the baseline for circulating endothelial cells is undetectable, and post-angioplasty, you can pick up 6 to 10 cells per cubic micrometer. If we can translate that to this kind of a model, that could be a very sensitive and specific indicator of vascular injury, and we need to look at funding research in this area.

VCAM-1, soluble beta thrombomodulin, P-selectin. Endothelin 1, also an important soluble factor to look at. PECAM, ICAM-1. And lastly, soluble FAS ligand. I think there's some data that's evolving showing that the endothelial cell death that I showed you in the scanning EM is probably associated with apoptosis and not necrosis. A lot more work needs to be done in this area, but if that is true, we might be able to detect soluble FAS ligand in the plasma as an acute marker of endothelial compromise.

Additionally, with regard to biomarkers and other "omics," as Dr. Doull refers to, I think there's tremendous opportunity here to look at the cells involved in the pathogenesis of these lesions for different expression patterns of different messages, different proteins, and so on. I think there's great opportunity here to do that if we can put together the right mechanism.

Funding. Critically important to the success

of our mission, and it's very early days yet in my committee. To be quite honest, we're struggling to figure out how to accomplish this, and we're looking for guidance from your committee. I have made some phone calls to NIEHS and there are potential funding mechanisms there, and I've been speaking with Ray Tennant and one of his colleagues. Yesterday I spoke with Denise Robenson at ILSI. ILSI does have a reputation of developing large projects like mouse tumors and hepatotoxicity and so on and funding them. They would be interested to see an application. That's just a beginning, unfortunately.

I think eventually we would anticipate Pharma would be interested in providing funds to support research in this area, but it's early days yet. Any advice or thoughts you may have, I would be appreciative.

With regard to funding, then, whatever the mechanism, I think we need to be looking at animal model development. As I said early on, the current animal models don't really predict what actually happens in humans, and what our current animals predict is something that we think doesn't happen in humans, but we want to prove that it doesn't by developing the right biomarkers. We need animal models that predict what really does happen in humans, and I think this is an area of research that we might look into, as well as the biomarkers.

We need novel and specific markers of endothelial and vascular injury that can be validated and reduced to practice. The monies and the research efforts will go into doing this.

Our immediate plans. We have a conference call lined up for the 31st of July to continue our discussions and expand and explore what I'm telling you today. I think we need to submit an ILSI application, if that's what the committee wants to do. I haven't mentioned this to my committee yet, so I need to review that with them. We need to look at the other funding mechanisms through NIEHS, which we're actively exploring. We're looking at setting up a workshop in collaboration with the ACT and/or the SOT meetings coming up in the fall and spring of '01 and '02. At the SOT meeting in '02, we have already organized a workshop on vascular toxicity and biomarkers. Dr. Schwartz and I are co-chairing that, and that is on the slate to be presented and we hope to organize some sidebar meetings around that for a broader participation and discussion.

There are the IP issues that I mentioned before that we are looking to understand more clearly. Maybe it isn't an issue, but we need to understand it more clearly. We need to understand the issues of confidentiality so that we can communicate more effectively between the agency to understand clearly what the issues are, what they see if

possible, and how we might help. Validation strategies are also key.

So, lastly, our recommendation then is that this particular topic does warrant the investment of further energies and monies to bring new biomarkers to the table that we can use in preclinical and clinical medicine. The methods need to be noninvasive. They need to be robust. They need to be specific. They need to be sensitive. And we need to be able to reduce them to practice so that we can translate them to phase I.

Thank you. I'm happy to answer any questions.

DR. DOULL: Thanks, Bill.

Our other working group is the cardiotox working group, and Dr. Gordon Holt is going to tell us about activities of that group.

DR. HOLT: I'm very pleased to be here to present our findings. From the moment that we constituted, it was, from a personal standpoint, a great relief really to find that we had been constituted with a good group with diverse experience from Pharma, academia, and then the governmental backgrounds to help us with all the ins and outs of things that we needed to consider, as you can well imagine.

Perhaps you're hearing between the lines right now, that frankly, to a certain extent, our work is in

progress. Our particular charges are likely to change in tune as time goes on. Our particular goals are likely to change as well, too.

I wanted to emphasize, too, that Ken Wallace wasn't able to be here today to serve as chairman in talking to you about what is going on, so I get the privilege, since I live 10 miles up the street.

Major points to be considered, as Dr. Kerns has just described. In all cases it's very much needed, we found quite quickly, to make sure that we're talking the same language and that we believe we're sitting at the table for the same reason. After we did that, we were able to come up with key questions, what we thought were the real pressure points for the information that we needed to gather to address our charge. We came up with some specific things that we can be doing in the very near future to address these charges, and I'll talk about each of those in time. Then we also started amassing a list of resources that we were quite clear that we did not have that we'll be looking to the committee at large for input on how we can do these things.

Again, I emphasize this is work in progress, and if I say something that seems challenging, then I really strongly encourage everybody to bring it to our attention so we can move quickly toward some tangible outcome.

In terms of our charge -- this was given to us -- identify opportunities for collaboration, develop valid markers that effectively predict drug-induced myocardial toxicity. We quickly tuned it a bit. What we believe we're trying to do is to find a path for implementation because that, as far as we are able to identify, does not clearly exist right now. So, find markers, find a path to implement them, at the same time clarify what the benefits would be of doing this action, and then finally to identify resources that are needed to bring this to bear.

In terms of getting our language straight, one person's biomarker is another person's target, so we had to be sure that we were working in the same zone with our language. We quickly discerned that there are biomarkers we could break down into major categories of susceptibility, exposure, and effect, and then subdivide it further. It's quite obvious that it's a matter of semantics. You kind of run out of words to separate the difference between exposure and effect.

Nonetheless, we believe we're down at the bottom end of the spectrum where we believe that we should be focusing our attentions on effect, in particular effect that takes a patient or an animal from a state of integrity, wellness, homeostasis, into something that is not that, stress, and perhaps injury/damage. And

injury/damage in our minds is that next step where the patient, whether it be a preclinical animal or a human, has actually had some effect that is long-lasting and adverse to the animal.

We wanted to also figure out what the characteristics of an ideal biomarker are. We discerned that we needed to have some idea of a goal in mind for what we were shooting for. I won't go into this list in detail. It's just here as a matter of record, and I emphasize ideal here. This is clearly a wish list because I think in many circumstances we and regulatory agencies will have to take what they get, what biology presents with. But generally speaking, I think there's probably going to be useful agreement that any biomarker will have to be specific to toxicity. It has to be sensitive, predictive, robust. There's no point in going through these things if all the work has to be done in a very expensive academic or very high IQ setting. That's just not going to hold true.

As you just heard from Dr. Kerns in the case of vasculitis, this is going to be a very challenging issue, whether preclinical and clinical markers will bridge both forward and backwards n the case of vasculitis. It looks like it will be less of an issue with cardiotoxicity. There are examples that do bridge already. And then ideally these would be noninvasive. In the case of

cardiotoxicity, it's an important point to stress that you don't want to induce cardiac damage in trying to monitor it.

Key questions that we came up with are listed here. I'll briefly touch on each of those in turn. What cardiotoxicity markers are already accepted? Can we look to existing models and get a paradigm in place for what we should do next?

We believed that we had to split that into two zones. One is what the FDA has accepted, and then what the toxicology research, academic, and industrial community is doing right now. Those are two different commodities, we felt.

How are new biomarkers quickly identified and validated? How can they be quickly identified and validated? There is an existing committee, the ICCVAM committee, that we looked to for some guidance on paradigms for bringing new markers on board. We also looked to the toxicologist community to help us with this task, and we are, in turn, addressing both of these. I'll talk about that briefly.

Then also, as you've also already heard from Dr. Kerns, we have considered what the FDA could do to enable this process, and particularly with confidentiality and some kind of funding vehicle.

So, with respect to the current cardiotoxicity biomarkers, I can just summarize a lot of work that we did in our two days of sessions in trying to identify whether or not there are existing guidelines. It looks like there are no biomarkers for toxicity. Again, we're talking about serum markers or something like that that's validated. QTC is not covered under our charge as a biomarker, so we didn't consider that further.

So, the FDA doesn't have an accepted guideline. How about the community? In fact, I should register there was a certain degree of surprise because there are some biomarkers that I'll talk about iin a second. Troponins are really highly regarded by most toxicologists as very good markers of toxicity, but they're really not. I'll put that forward. There is quite a long shopping list that we went through, that I just listed here for your information, of proteins, changes that are well known, or at least somewhat well known, in the literature to be associated with cardiotoxicity. But we concluded quite quickly that troponins are by far and away the most advanced of any of them. They are approved for some aspects with myocardial infarction in the regulatory community, but not for cardiotoxicity.

The key thing here is validation. With all these markers, how can this information be bridged into the

regulatory setting? It's all about validation and some kind of consensus-reaching.

I'll also emphasize, too, that we had a strong sense -- and in fact, to a certain extent, personal knowledge -- that these "omics" are in fact in the wings and they have identified very, very compelling markers, and we want to be able to bring this information on board for us as well as to help advance that so that it's a community-wide process.

Again, we feel that while there's probably lots of statistically significant identifications that have already been made out there, that again, even without knowing more about what's going on there, that they too will face a validation problem.

So, how to validate? The group is looking for models to help us to identify how validation already occurs, and also how we might suggest that things go on in the future. The ICCVAM, the Interagency Coordinating Committee on Validation of Alternative Methods, already exists and has a very important role in bringing new marker paradigms into regulatory acceptance. These tend to be investigator-driven. That is, the person comes forward and says, I'd like to get acceptance on this.

They have a very well-described path -- not so much a path but a set of attainments that they look for

markers to be advanced to, both in animal testing and human testing, frankly quite an involved process. The difficulty as we perceived it is that it wasn't as clearly milestone-driven as one would have hoped, and it had a certain degree of all or nothing policy to it. But nonetheless, it's an important guideline for us to look to to see if there's a way to help bring things to regulatory acceptance. We very much hope that the ICCVAM members will help us to explore if there's any possible interface between this group and our group to see if we can bring things forward.

We also looked for methods where we can get a consensus finding information from the toxicology community, and we have particular example that we propose to do this already. These may well be driven by expert working group people. Many people in the group, we came to find out, know people who know people who can basically bring some of the power of the toxicology community to bear on the kinds of things that we're interested in.

We hope to be able to establish some kind of expert consensus on specific biomarkers. This is probably not going to be a huge finding exercise, but in fact a very specific method.

We propose using toxicology conferences as forums. These are public forums with speakers and platforms, discussion, the usual sort of things that go on

in these conferences, to reach some kind of a gathering of information that will eventually lead to a report. And our working hypothesis right now is that that will be akin to an NIH consensus conference. Not binding, but just a way of collecting information.

That's very effective for the kind of information that's already in public domain. What it does not address is the information that we have a strong sense and, to a certain extent personal knowledge, of markers that are out there that the new markers, with the new technologies that have recently come online, where these discoverers and innovators were likely to require maintenance and nondisclosure to ensure their market preservation, at least to a certain extent of time.

How can that be dealt with? It's going to be complicated because there is clearly going to be some complexities with multi-party confidentiality. We don't have any suggestions for how to deal with that other than to say we're heartily enthusiastic to do what we can to help in any way to bring that to bear. Perhaps there is some subgroup forming that we can bring at least some information into a private forum so we can make sure that we're seeing the best information available.

As Dr. Kerns has already talked about, there's almost certainly going to be some need for funding

resources. The idea here is that you probably need to have something to help support academic researchers to focus on specific things that the agency and the committees know they need to find more information on, and there's got to be some enablement there by some funding.

There also is likely to be some need for a clearinghouse, a warehouse of samples and standards too so that everybody can be testing to the same methods and qualities. There may come a time when there's a need to have a specific independent testing method done to make sure that everything is going along as it's supposed to be.

How's this going to be accomplished? Probably industry and PhRMA should be looked to. I think even as an industry member myself think that industry should be footing some of this bill. It's really no different than a patent application. If industry knows what's supposed to be accomplished, what will be accomplished with success, then they can help work that into their cost of doing business.

Certainly the existing granting agencies and the NIH universe are also a great place to do some of these things. It will require some integration.

And last but not least, the FDA hopefully can bring some resources to bear on this.

What tangible things can we do that we are

doing right now to move things forward? We are holding, internal to the expert working group, although it is open to the public, a troponin workshop to be held, I guess, here on the 29th. This is again focused on troponins. We will be reviewing existing data. We will be trying to identify data gaps in the validation pathway as we see it, and then we'll be drafting suggestions on how to take troponin as a particular example of a new marker that we believe can be brought on board or, at the very least, can be put through paces that will let us know whether it can be brought on board.

Secondly, we have already taken the privilege of having some contacts within the group to conduct a fall workshop at the American College of Toxicology specific mostly to troponins. We've already scheduled this and started looking for speakers. This, of course, will be conference attendees, where there will be a presentation of current biomarkers on myocardial injury, again heavily weighted towards troponins. And then we are anticipating that there will be some sort of a satellite working group meeting, again that should be open to the public, to review the status of troponins and also to update on novel reporters. That may well be a time when we're going to need to start addressing confidentiality.

What's the outcome of this? We really do

believe that fairly quickly we can at least prioritize the markers that are out there right now for bringing them online to help with better understanding of toxicology, cardiotoxicity. We also believe that the outcome of this is we will be able to set up a help form of paradigm for bringing new markers on board too.

I think I'll stop at that.

DR. BYRN: Thank you very much.

I think because of time, are there any major questions anybody would like to ask of any of these two speakers?

DR. DOULL: I think our intent was simply to inform the committee about the kind of science that's going on and to acquaint you with some of the problems that the working groups have already brought to bear, which our committee, of course, will deal with in its future meetings.

DR. BYRN: Thanks very much, John.

Helen is now going to give a sort of overview or a what-next talk on these two issues.

MS. WINKLE: I'll try to make my talk real quick, since time is limited.

I do want to say to Dr. Doull, though, that I agree with the word "leveraging." I don't consider this leveraging it either. I consider it more partnering. I've

always had a difficulty with that term, so I thought about it long and hard, too.

I want to thank Dr. Kerns and Dr. Holt for coming and giving us this overview of the expert working groups.

Just to remind the committee as to what these groups are responsible for, they're basically fact-finding groups for the subcommittee. They will bring the information that they come back with to the subcommittee, and the subcommittee then will, in turn, make recommendations to the full committee.

As I think most of you on the committee know, Dr. MacGregor was basically the champion of this subcommittee. He's worked very hard with Dr. Doull and others to get the subcommittee up and running. Also I think it's already been mentioned by Dr. Doull that Dr. MacGregor has left CDER and gone to NCTR.

At that time, there was some question as to what should be the future of this subcommittee. So, I want to talk a little bit about that just so you as the advisory committee will know what our thinking is in the agency. Dr. MacGregor and myself talked many times with Dr. Woodcock and Dr. Casciano on this subject and have really been looking at the concept of possibly moving this subcommittee under the auspices of NCTR.

Basically the purpose of this committee, which I think Dr. Doull has already addressed, is to provide advice on improved scientific approaches to nonclinical drug development and to foster scientific collaboration or partnering.

Here are the objectives. I won't go through those. I think we've already talked about that. I basically want to talk about the future of this committee, as I said.

The committee will continue to focus on nonclinical safety assessments. We think this is very important. It's something that's very important to us at CDER. NCTR has a mandate and structure to lead in this area, so as I said, we've been having conversations within the agency as to whether to move this subcommittee under the affiliation of the NCTR Science Advisory Board, and basically too those conversations have included how this affiliation should be accomplished.

We've talked about the advantages of the transfer of the subcommittee. Already the subcommittee's liaison, Jim MacGregor, is part of NCTR. Also the ICCVAM process, which has already been mentioned, in the agency also resides in NCTR. NCTR is oriented in doing toxicology research, and it has the resources to support that research. They also have a scientific advisory board,

which has experience in supporting such working groups as this.

And I may want to just back up a few minutes to talk about CDER's position on research. I think that most of you on the subcommittee know that our resources dedicated to research are limited in CDER. So, we feel that NCTR is in a much better position to support any of the research that comes out of these working groups. Basically they also have the resources to support the working groups. And NCTR -- I talked to Dr. Casciano on numerous occasions -- really has the interest of being involved more in this area.

However, should we decide to make these decisions, we feel that CDER is still going to play a very important role in the future of this subcommittee and with the recommendations that come out of this subcommittee because most of this is affecting how we make regulatory decisions on pharmaceuticals.

So, we will continue at CDER to support the NCSS if it is moved through participation in working groups. Based on the recommendations we'll bring issues relating to research and regulatory issues to the advisory committee so that we can have further discussion on these issues as they relate to our regulatory process. CDER will bring regulatory questions to NCTR's Science Advisory

Board, as appropriate, that relate to this subject.

So, we still feel that we'll play a very active part in the role of this committee, should it move to NCTR. We see this committee as very important in helping us set future standards, and also see that there are important things that will come out of this subcommittee as far as our guidance development.

Basically where to from here? NCTR has not finalized a decision as to whether to adopt this committee as one of their own. They're convening a team right now to review the appropriateness of the subcommittee and make a determination whether it should, in fact, become a part of the Science Advisory Board. CDER will receive a report back from that team. Dr. Casciano said that he would hope to give this to me in the fall, which we will then in turn share with the advisory committee.

Until that time CDER will continue to take on responsibilities for this subcommittee. There are a lot of things happening with the subcommittee, including workshops, working groups, meetings, et cetera, and we'll continue to support those until a final decision has been made. So, I don't want you to think that this is sort of going to go down the tubes if we do make this transfer. In the interim, we'll continue to support it, and after that we'll be an active part.

Any questions, comments? Yes, sir.

DR. MARVIN MEYER: The focus of today's discussion seemed to be toxicology. Are there other issues that aren't toxicological that would fit within the Nonclinical Studies Subcommittee, and will they fit at NCTR?

MS. WINKLE: That's a good question. I think if we come across other issues, we'll have to make some decisions then how we want to handle them internally, if they're not toxicology issues. Right now, as you can see, all the issues that have come up are in the toxicology realm, but you're right, there are other questions that could arise.

DR. MARVIN MEYER: I'm thinking perhaps some of the issues from the bioequivalence side, with ways to determine permeability of drugs, in an in vitro setting. That wouldn't really fit necessarily with NCTR.

DR. WINKLE: Right. And we would probably bring those issues independently to the advisory committee.

Any other questions? Okay, thank you.

DR. KERNS: I just had a point for clarification. So, as I understand it, we're to do nothing different in the interim. We just proceed.

DR. WINKLE: That's right. Just proceed. And we'll continue to support you. We feel the work is very

valuable, so we don't want it to sort of fall to the side while we're making this decision.

DR. KERNS: And you'll deal with the politics.

DR. WINKLE: Right. We'll deal with the politics.

DR. BYRN: It sounds like the prospects for funding at NCTR are more advantageous than FDA. So, that could be an advantage to the investigators.

Is there any committee discussion on this issue? Any additional questions, concerns?

DR. DOULL: I might just say, Steve, that the subcommittee was, of course, very concerned about maintaining the link with CDER because we feel that what we do in this committee will have great impact for writing guidelines and regulatory approach and so on. So, we need a very strong link and a very effective link in order to make those things benefit in a two-way kind of situation, so that our feeling is that we are very concerned about this and we'll follow this very closely and, hopefully, can work out something that benefits us all.

DR. BYRN: Let's go on to the next session. I think we'll just go ahead. I had some discussions about whether we could break this up, but because of other meetings, I think we'll just go ahead until the CMC section is done. So, Dr. Chiu will start out and give us an

overview of the CMC section and the AAPS workshop.

DR. CHIU: We are here to give you a progress report of this new initiative, the risk-based CMC review. We also are here to seek your advice on two questions.

Just to refresh your memory, we brought this topic to you last November, and this is a program with a three-tier process. We are actually in tier 1 of this process. Tier 1 is to establish scientific attributes and acceptance criteria for drug substance, drug products, microbiology, and CGMP, to define what is considered low risk with respect to product quality. With these attributes and acceptance criteria in place, we would be able to compile a list of low risk drugs.

Then the second tier is we would show this list to our medical colleagues in CDER and ask a determination of a safety factor, whether any of the drugs on the list should not be considered low risk from the safety perspective.

Then the third tier would be evaluation of the GMP status of individual firms, and to see whether a firm would be eligible for this program.

A drug, if it is under this program, then the agency will have less oversight. There are three elements.

The first one is we will minimize the types of post-approval CMC changes requiring a submission of prior

approval supplement, for changes-being-effected supplement.

We will reduce the amount of CMC information needed to be reported in annual reports to our approved application.

The third one is if the drug is on the list, then if a genographer would like to make a copy and this firm has good GMP historical status, then we will reduce the amount of CMC information needed to be filed in an original ANDA. We call it a truncated ANDA, and this ANDA will mirror the amount of data required in an annual report for an approved application.

So, we have many internal discussions. We presented this to ONDC scientific rounds, and we had brown bag meetings numerous times internally to seek comments, inputs. As I said, we talked about this last November in this committee. In June of this year, we presented this program to AAPS workshop. We had a one-day full discussion from the participants, and we seek their scientific input, how to put together the attributes and the acceptance criteria. Therefore, we can start to compile the list of low risk drugs.

So, today we're going to give you four reports on what happened in this workshop. We will cover drug substance, drug product, microbiology, and GMP. The speaker for GMP, Ms. Pat Alcock, could not attend, so

therefore Dr. Eric Duffy will be her substitute.

DR. BYRN: Eric, as we go on, I would like to introduce two invited guests for this session, Dr. Leon Lachman and Dr. Gary Hollenbeck. And our guest speakers are speaking. Of course you just heard from Dr. Chiu, and now Dr. Duffy will be speaking, and then Dr. Sayeed, and Dr. Hussong. So, Eric, please proceed. Thank you very much.

DR. DUFFY: I'd just like to give a very brief overview of the discussions that took place at the AAPS workshop on drug substance issues. We had a brief presentation in the morning, to try to frame some of the issues, and then multiple breakout sessions, which were very active and really quite productive.

Overwhelmingly, the participants felt that the major criterion that would define "low risk" with respect to drug substance manufacturing was the manufacturer themselves. What are the capabilities of that particular manufacturer? Are they capable? Do they know their process? Can they reproducibly manufacture the product? These seem to be the recurring themes in most of the responses from the industry participants.

Secondly and close behind the quality parameters of the manufacturer themselves was having adequate specifications and the capability for adequate

quality assessment. This seemed to be a recurring theme as well.

Lower down on the scale of critical issues seemed to be issues of stability, inherent stability of the particular drug substance. What the discussions pointed out was that people felt that if you really understood the inherent stability of the product itself, that would seem to be adequate, a good understanding. The discussion centered around whether a drug substance which is flat-line, no degradation, would that be the paradigm. Or would it be acceptable if you had degradation, but if it were well understood and predictable? Would that be acceptable? Well, people tended to think that the latter might be an acceptable paradigm with respect to stability.

Some of the issues that we had brought forth in the presentations at the beginning of the workshop had to do with whether one could define complexity of structure as a parameter that one might use as a measure of low risk versus otherwise. And I think people's consensus was that the degree of complexity may not necessarily be of any relevance. Furthermore, how one would define complexity seemed to be extremely difficult, and I think we have struggled with that particular issue as well in other contexts. But the degree of complexity is not relevant because primarily there are analytical capabilities,

regardless of the degree of complexity, to understand the quality parameters of the particular drug substance.

Another issue that we had brought forth was whether one could use manufacturing process complexity as a parameter to define a drug substance which might be of low risk. The consensus I believe was that it really wasn't necessarily a defining criterion, but simply that the process should be well understood, that the manufacturer should understand their process. And this hearkens back to the initial point that I made, that it really depends upon the manufacturer and their degree of understanding of the process. It was considered essential that the manufacturers themselves understand exactly the complexity of the process and have it well controlled. Another reason for really not regarding this as a defining criterion would be the difficulty in defining what constitutes a complex versus simple process.

One other criterion that we had considered was the inherent reactivity of a drug substance. Is it robust, or is it susceptible to reactivity with atmospheric and environmental issues? Or would it be sensitive to various formulation excipients, et cetera? This was considered to be something that could be quite reasonably assessed in the context of the drug product itself, in terms of its stability.

Some of the other issues had to do with quality measures. Primarily the discussions focused on specification. It should be well justified. The set of specifications, the tests and procedures should be well defined and justified. And typically for drugs that have been around for a while, in most cases the specifications should be upgraded to contemporary practice and guidance.

There were, however, some concerns expressed by many of the industry participants having to do with the notion of upgrading specifications and maybe test methodologies where one might observe, for example, in an enhanced impurities test or assay, new impurities arise. The concern was expressed that if one did observe these new impurities, what would you have to do? Would a new safety qualification have to be conducted? Would toxicology considerations have to be considered? There were some concerns based upon that and there were a number of people who said that a more clear definition of in-use qualification from a safety perspective would need to be put forth by the agency. So, this is something that I'm sure we will have to consider.

With respect to the set of specifications as the measure of quality, it was considered appropriate by many participants that that may not be sufficient for assessment of change, impact of quality on change, sort of

in the realm of BACPACs, where one needs to assess the impact of a change in manufacturing that is made, and maybe a set of protocols would be appropriate to establish with respect to assessment of change.

With respect to process characteristics, I've mentioned that it was considered essential that the process be well understood and controlled, and that also a set of in-process controls need to be in place, and that those controls need to be well justified. In terms of process characteristics, simple versus complex. As I had mentioned, it was considered not particularly relevant, and the definition of how one would do this is, furthermore, very difficult. Would one define it in terms of yield, number of process steps? The type of manufacturing process, very difficult to define. It was overwhelmingly considered that the process should simply be robust. Now how that's defined is another issue.

There were some concerns expressed, and I've listed a couple here that some of the manufacturers had a concern that if a drug was put on a list, would it then be mandatory that they engage in this process, upgrading the specifications and going through whatever registration process there might be. That would certainly have to be considered by the agency. Furthermore, if a drug was put on the list, would the agency promulgate kind of a

monograph where there would be a universal specification? There was some concern about that.

That's really about all on drug substance. Steve, we're going to take questions afterward, or shall we do it now?

DR. BYRN: Maybe because of the number of speakers, we should do it now, right after each speaker. So, are there any questions for Eric? Gary?

DR. HOLLENBECK: Sort of three questions, Eric. First of all, this process, the streamlining process, relates to drug products. Is that not correct?

DR. DUFFY: Well, one of the issues that did come out in the discussions that wasn't necessarily specific to drug substance breakout sessions was the notion of whether or not one could have a drug substance considered to be low risk, but the drug product that it's used in is not considered so, or vice versa. That is certainly something that needs to be discussed. I'm sure Vilayat is going to mention something about that as well. But yes, we need to decide whether you can split it.

DR. HOLLENBECK: So, you are not talking about changes in the manufacturing of the active in this context?

DR. DUFFY: Oh, yes, we would be.

DR. HOLLENBECK: You are talking about that.

DR. DUFFY: Yes, and certainly the BACPAC

initiative would go a long way toward addressing the issue of change in manufacturing process. I think we have to think about whether or not the BACPAC initiative would need to be enhanced in any fashion for those drugs that are on this low risk list or not. It's something we haven't fully explored.

DR. CHIU: Originally we were talking about drug product, drug dosage form. However, because drug substance is part of the drug product, of course if the drug product is low risk, then drug substance must be also low risk. You cannot have a high risk drug substance and have a low risk drug product. We think the two are linked.

However, we did receive comments we should consider if the drug substance is stable, but if the drug product, the dosage form is not stable, then we should not just forget. And then we could have a program, drug substance part can be low risk. So, that's something internally we have to discuss.

This program is not about post-approval changes because once it is on this program, there's no preapproval CB supplement anymore. So, therefore, the BACPAC does not apply at all. There's no need to report those changes.

DR. DUFFY: You said you had a few questions, Gary.

DR. HOLLENBECK: Yes. I guess just following

that up, I guess there was a presumption, at least for me, that we would always be using quality active pharmaceutical ingredients, and that the danger of establishing new specifications for them in this context really wouldn't help streamline the process.

DR. CHIU: For the initial program, of course we will only consider stable bulk drug substances. We will not include the proteins or other labile substances. However, the industry's view is it really doesn't matter if it's unstable, as long as you know the degradants, you know the degradation process, you know how to control it, you have a good specification to detect degradants. Therefore, they should not be out of consideration.

DR. HOLLENBECK: My other main question. When I saw this category come up, I kind of expected some consideration analogous to SUPAC, the permeability, solubility, therapeutic kind of screen for active ingredients as part of the classification system. Is that involved at all?

DR. CHIU: Of course, the BCS classification could be used as a consideration, but we think you should not be limited to the class 1 because other substances which may be not soluble, not permeable as well, but from a quality aspect, they are probably low risk.

DR. HOLLENBECK: It kind of gets to what Yuan-

Yuan had mentioned in her presentation, is that the considerations presently are the tier 1, which are quality attributes and other performance and in vivo performance attributes are a different consideration.

DR. BARR: Basically does this group then relate just to the stability and perhaps sterility of the unit, as opposed to the release or the performance? Because I'm kind of confused. I think like Gary that it's very difficult for me to separate what's already been done in SUPAC and the bioequivalence classification and those kinds of things to identify problem drugs and non-problem drugs. Apart from the stability, I don't see much difference between the two. Could you clarify that?

DR. DUFFY: In terms of product performance, that's the object eventually, how does the product perform in use. Now, certainly for drug products that would be subject to performance problems due to quality attributes, that would certainly be a major consideration for us. Vilayat is going to mention a bit about that in his presentation. So, ultimately that's the prime consideration, how the product actually performs.

DR. BARR: Perhaps a low risk drug would be a drug which had excellent stability based upon some set of criteria, and would meet, say, pharmaceutical classification class 1 or something like that. Is that a

fair statement?

DR. DUFFY: We're not necessarily considering the BCS as tied directly to the quality attributes. We're really focusing more on manufacturing capability, whether the product can be manufactured in a consistent and predictable fashion. Is the drug product itself robust, is the drug substance itself robust, where the degree of FDA scrutiny over manufacturing issues would be considered to be maybe passed over to the manufacturer, provided the manufacturer has the capability to provide proper controls. It's really that approach.

DR. CHIU: I would like to add. This program is just to reduce the oversight of FDA. It does not reduce the responsibility of companies to make assessments whenever they want to make a change, whether the change will impact the product performance, product quality. They continually have to do those things, and they just do not need to provide the documentation to the FDA, paper documentation or electronic documentation.

However, we also plan to have a joint inspection. Periodically we will go to the site and inspect and make sure companies continue to do the things that they are supposed to do.

DR. DUFFY: I'm going to say a bit more about it when I talk about GMPs, but that's an integral part of

this whole program, that the manufacturing capability and adherence to GMPs and having quality systems in place on the part of the manufacturer. It's a quality issue primarily.

Any further questions?

DR. RODRIGUEZ-HORNEDO: Yes. In the case of solids that are drug substances, were any specific scientific attributes considered beyond what you presented, such as solid state structure, functional groups, melting points. I wonder if there is a similar paradigm to what has been used in the bioequivalence, biopharmaceutical classification system to the vulnerability of a solid in meeting the expectations we have with respect to quality beyond what you have mentioned here.

DR. DUFFY: Yes. Certainly physical attributes are very important, and some physical attributes are well understood and well controlled. And others might be less easily understood and controlled. Polymorphism, for example, very important, but might quite easily be controlled and understood. Less well understood might be particle size distribution, where that's important for the drug product performance.

What constitutes a defined particle size distribution and how does one assess the change in that particular size distribution is a difficult thing, and in

fact we're hoping that some of the initiatives that PQRI on that score can really help the industry and the FDA come to an understanding of what constitutes a good understanding of particle size distribution.

But you bring up a very good point that the physical attributes certainly can't be neglected in terms of assessing whether or not it's a drug substance. It might be vulnerable to vagaries of manufacturing problems or atmospheric problems.

DR. CHIU: I would like to add. Polymorphism and particle size, all those things were discussed in the workshop. However, the feelings of the participants were although those are important attributes, as far as they are analytical tools to define them, to detect the change, then they should not be used as a barrier for defining low risk drugs.

DR. RODRIGUEZ-HORNEDO: I thought the objective was to also reduce the regulatory burden. We also have very good techniques to identify the bioequivalence, and yet the impact of the biopharmaceutical classification system is there.

DR. CHIU: Let me add, because if it affects the bioequivalence, then the case is requiring in vivo studies, we're not removing that oversight because based on FDAMA, whenever there's a need for in vivo studies, it

needs a prior approval supplement. So, we must comply with our law. So, therefore, your concern is that this will change FDA with our oversight, then if you affect in vivo performance, then we will not know, that won't happen because it would still need prior approval supplement when in vivo bioequivalent studies are required.

DR. DUFFY: Yes, Dr. Anderson.

DR. ANDERSON: If I understand this correctly, the most crucial element of this whole thing is the manufacturer.

DR. DUFFY: That was the consensus of the participants at the conference.

DR. ANDERSON: I'm not questioning that. My question is, will you have some criteria or some standard, some kind of guidelines for deciding in this area?

DR. DUFFY: I'll be getting to that in the GMP discussion, but the short answer is yes.

DR. ANDERSON: That's good.

DR. DUFFY: You like short answers.

DR. ANDERSON: Well, my students always give me short answers.

(Laughter.)

DR. ANDERSON: Under your quality controls, underneath the upgraded to contemporary guidance, what happens if new impurities are discovered in the drugs?

DR. DUFFY: Well, this certainly was an area of concern that the industry had expressed. It's always a safety issue. If one finds new impurities, you need to assess the impact that it may have upon the safety profile of the drug. How one does that is something we do need to work out, and the discussion of in-use qualification is one thing, but there is the standard ICH approach to qualification from a safety perspective. These issues certainly need to be addressed. There's no question about it. There is tremendous concern on the part of the industry.

DR. CHIU: Let me add. If we have a drug on the low risk list, even though we reduce the oversight, but if the company makes a change, new impurities occurred because of the change, because of the change of that kind, it will affect the specification because when you have a new impurity, you will have a change of specification. You need a test or you need a change in the substance criteria. Therefore, a change in specification under FDAMA requires a prior approval supplement.

So, therefore, we will still have oversight when a new impurity is discovered. The firm needs to submit a supplement. We saw the qualification data, tox data necessary. So, this program will not affect when a new impurity is discovered.

DR. ANDERSON: One final thing. Under structure, it is generally known that the analytical methodology is less reliable for complex structures than it is for simple ones. Under the process where you have simple versus complex, and you said that's considered not relevant, it is usually known that the more complex the process is, that is, the number of steps in a reaction, the more likely you are to encounter a lot of other problems, including additional impurities and things like that.

DR. DUFFY: Well, there is greater opportunity for things to foul up, yes.

DR. ANDERSON: I think this is under not important or something like that, but that may be something you want to look at.

DR. DUFFY: We are going to be considering that, indeed. What I maybe should stress is that my presentation and the following presentations are really an attempt to summarize what the consensus of the workshop participants was, and not necessarily the specific recommendations that FDA will have. These are considerations that we're going to take back and work on in our further deliberations.

Yes, Gary.

DR. HOLLENBECK: Not to prolong this, but would it be possible for a drug that's classified as a narrow

therapeutic index drug, given the comments that you've made, to be considered low risk? You've gotten into tier 2 of our considerations, which is discussions with our medical folks.

DR. CHIU: I'm sure our medical colleagues will not agree.

DR. BYRN: If I can just give you an idea of what we're going to do now, based on our agenda and so on. We're going to go until 12:45, so if we can adjust the presentations and such. We had a lot of discussion right now, and we'll try to compress the committee discussion. Then we'll break for lunch at 12:45 and will come back with our open hearing at 1:45. So, everybody got about the allotted time.

Dr. Sayeed is next. He's going to talk about drug product.

DR. SAYEED: As pointed out by Eric, the workshop was like a morning presentation followed by a breakout session. So, what I'm going to do is go briefly into what was presented in the morning session, and then go into the input we got in the breakout sessions.

In the morning session, these two distinct approaches were presented to the audience. As you see, the first approach was based on developing a set of attributes or criteria for defining low risk and use this set of

attributes, once they're developed, to identify low risk drugs. And the second approach basically deals with the knowledge and the understanding we have for a given drug product and identify these drug products based on the understanding we have, and then go ahead and perform a quality risk assessment to define low risk.

Given the nature of the approach one, which is basically a global approach, the determination was made to get the input from the audience on only this approach. There were certain questions that were raised in the presentation, and based on these questions, we expected a little bit of input in the following breakout sessions. So, I'm going to go over the questions and the attributes which were presented to the audience in the morning session based on this approach one.

Here I have a set of attributes which were actually presented in the morning session for the discussion in the breakout sessions. The attributes were dosage form, strength, manufacturing, specification, and stability.

On the next few slides, what I'm going to do is I'm going to go into each of these attributes and then go into the input we got from the audience for each of these attributes.

Dosage form. The question raised was, should

all the dosage forms be included in this risk assessment or in this initiative. The general consensus was, yes, maybe we can consider all of them, but it wasn't further defined what that maybe is. So, due to the time restraints and all that, the general thing was, yes, depending on the understanding, maybe all the dosage forms can be considered for this initiative.

The question for the strength was, should strength be used as a factor in determining risk? Should there be a line drawn below which a product can be identified as either high risk, or above a certain point, it can be identified as a low risk? The general consensus of the audience was, it should not be considered. Strength should not be a factor for defining risk in terms of quality.

Moving on to the manufacturing, this is where we spent most of the time. Almost all the issues relating to manufacturing were covered, including the physical attributes of the drug substance, the excipients, the interaction of the excipients with the drug substance, and the various manufacturing processes that can be used in manufacturing a given drug product.

Having discussed all of that, the input was, regardless of how complex or how difficult the process is in making a given drug product, it should not be used. It

really doesn't inherently contribute in defining risk. In other words, what the audience was trying to tell us was, if we understand the process, if there is a control and the process is controlled and validated, then the manufacturing should not be an issue in defining low risk.

But there is one thing which clearly came out in that session. If there's any functional packaging attached to the product that includes like a delivery system or something like that, then that product should not be considered as low risk.

In specification, the thing which was dealt with in specification was, is it adequate to just have the USP specs? Or for this initiative, should the specifications be updated to the current standards. The general consensus from the audience was, yes, there is a need to update that standard to the contemporary standard in order to adequately define or assess the risk for this initiative.

In terms of the stability of the product, again, the questions and the things which were discussed in the breakout sessions were, do you need to have a profile? Do you need to have a complete understanding of the mechanism of degradation? Does the degradation have to be predictable, or there should be some sort of a limit placed, and depending on the level of the degradation, is

there any way to define the product, whether it's a high or low risk, depending on the level of the degradation?

So, the general consensus was the level should not be a determinant, regardless of what you see in the degradation as far as you understand the degradation, as far as the degradation is predictable. The level of the degradant should not be a criterion in determining the risk. But the consensus was, yes, there should be an understanding for the mechanism of degradation, and the behavior has to be predictable in order to adequately define risk for this initiative.

The outcome of this discussion was, in summary, it's hard to define or identify quality attributes so that those attributes can be used for defining a product, whether it's a low or high risk. They said approach one is a good approach but it was difficult for the audience to actually pinpoint the attributes that could be used for defining low risk. They were telling us, give us a product and tell us what the product is and how it's being made, then we can tell you whether it's a low or high risk product. That was the basic outcome from the breakout sessions.

Thank you.

DR. BYRN: Questions for Dr. Sayeed?

DR. SHARGEL: Yes. I have perhaps a need for

clarification. When you're saying strength, are we really talking about dose in terms of a very low dose drug, maybe in micrograms with a large excipient concentration versus a drug that's a relatively high dose versus a very small excipient?

DR. SAYEED: Well, that was a question which was raised when we said low dose, if you have micrograms or milligrams, or something going into like 500 milligrams versus a microgram. The general consensus and the input we got from the audience was it really doesn't matter whether it's 1 microgram or 500 milligrams, as far as they understand the process, as far as the process is under control and validated. The strength should not be used as a determinant for defining risk.

DR. SHARGEL: May I have a follow-up? Concerning then the dose response -- and that may go back to the drug substance -- are you considering a drug in terms of nonlinear or having a very steep dose response versus one that's relatively flat, that small doses doesn't make much change?

DR. CHIU: No. The project is really only related to product quality. We are not talking about in vivo response. And if a nonlinearity response becomes a safety factor, we will evaluate in our tier 2 of the process.

DR. SAYEED: Are we going back into the clinical effects, and we really don't want to get there. That's part of the tier 2, and we're dealing with tier 1 only here.

DR. SHARGEL: However, if you were dealing with a nonlinear product, then small changes might affect its delivery.

DR. SAYEED: Well, that's something which will be considered, but what I'm trying to present here is what we got in the breakout session. It really doesn't mean that we're going to follow up on that but that's what we got there.

DR. BYRN: Any other questions? Leon and then Bill.

DR. LACHMAN: I think we're talking about trying to control these active ingredients and dosage forms by the measurement of the quality of the active ingredient and the product from a reproducible point of view. I think we have to consider the inherent characteristics of the active ingredients, the complexity of the synthesis and complexity of the molecule, as was indicated before, as well as the complexity of the process.

I'm sure you can control it. It doesn't mean that everybody can control it to the same degree. And I think that's where you run into a problem. I think in

order to have a tier 1 set of characteristics for active ingredient products, you're going to have to somehow cut the totality of the product mix that you're talking about here. If you're looking at the outcome of the workshop, I don't think you'll ever get to that tier 1 set of compounds and products that you can use. That's just an observation.

DR. CHIU: I think you made some good comments. This is a difficult issue because most of the companies think there are no high risk drugs. There are only high risk companies. And I'm not one of them.

(Laughter.)

DR. CHIU: At the agency we have to establish objective criteria. So, we will proceed from a scientific point of view.

DR. LACHMAN: What I'm trying to say here is we're going to have to consider the basic sciences here, physical and chemical sciences, not just the practicality of coming up with a dosage form. If you do enough work, I'm sure you'll come up with it, but the amount of controls you're going to have to implement to assure the repeatability of that is going to be enormous.

DR. SAYEED: That was the intent of the workshop, to get some input like that. But unfortunately what we heard was, for a given company if the process is under control and if it's validated, we are fine. As Yuan-

yuan mentioned, there is no high risk product. It's all a high risk company.

DR. BARR: It seems to me that the ideal goal, that what you're really seeking is to try to find those few substances which may be so stable, so safe, and be so easily manufactured that you can reduce the amount of work that you have to do. That would be tier 1, as I understand it. You have to use simply physicochemical measurements and characteristics to put them into tier 1.

Most drugs I think are going to fall into a category in which to some degree they're going to be dependent on some of their pharmacologic properties and their critical manufacturing variables. There, just to comment on one point just as an illustration, the dose and the strength is very important. I know at least two companies that have had great problems manufacturing levothyroxine because of the very low dose and the difficulties of manufacturing it. That to me is an inherent difficulty, and the minute I would see a microgram dose, I would say, somebody's going to mess up.

DR. SAYEED: I totally agree with you.

DR. BARR: And next, we have to get into somehow the pharmacologic linkage to that.

And then it seems to me the next linkage is the dosage form linkage. Obviously, stability in an oral

tablet is going to be different than the stability for intravenous products that maybe have to be sterilized. So, the dosage form is going to be critical.

But it seems to me that ultimately what you'll need to do is to come up with the critical manufacturing variables for that particular dosage form, maybe for that particular company, but maybe in general, and then define the stability or the range of stability about that critical manufacturing variable, whichever they are. In other words, how sharp that peak is on that variable, or how flat that is and how much area you can have on either side of those variables. I think that probably is workable.

DR. DUFFY: You mentioned probably the poster child of problem drugs in levothyroxine. Not only is the drug substance itself problematic, but how you then formulate it. It's probably one of the more difficult you could come up with. So, that's the kind of consideration we certainly would be making. Is the drug substance itself inherently stable, and is it subject to problems depending upon how it's handled and how it's manufactured? That example was very well put.

DR. BYRN: Now we're really running out of time. I'm not sure how we should do this. Maybe try to do it like the next two talks in two minutes apiece or something.

(Laughter.)

DR. BYRN: If we could do that, and the committee also may need to limit their comments a little bit or we'll never get to lunch. We'll just start our hearing.

DR. HUSSONG: Good afternoon to all my hypoglycemic friends here.

(Laughter.)

DR. HUSSONG: The AAPS conference on streamlining the CMC regulatory process had two sessions on microbiology issues, one concerning the post-approval changes to applications and the other was to try and define specific characteristics to qualify drug substances and drug products as low risk. The discussions focused on sterile products, but we also got some comments concerning non-sterile products.

Now, participants felt that sterile drugs could be separated into risk-based groups based on sterilization processes used in their manufacture. For example, the terminal moist heat sterilization processes were considered to have greater reliability than the aseptic processes for manufacturing. Although this generality was noted to have exceptions, aseptic processing is universally agreed to offer greater challenges.

Certain changes to the processing of what might

be considered low-risk products will still require supplements, however. These examples might include major changes in sterilization technology. For example, if you were switching from filtration to gamma irradiation.

Additionally, if you were deleting steps in the sterilization process. For example, if the sterilization process used aseptic filling methods, followed by a short heat process, and if you dropped one of those, that would certainly require a supplement.

Also, changing critical parameters in the specifications concerning the sterilization process. Those would be the control parameters for the sterilization.

However, many changes, about 20 of them, were noted that do not negatively affect sterility assurance, and for these it was recommended the route of annual reports could be used. Now, some of these included minor changes to container and closure systems. Also offered as an example were equipment items used prior to the sterilization steps. Additionally, terminal sterilization autoclave loading patterns were felt to be kind of low risk concerns. And several people argued that the lyophilization cycle really didn't have that much to do with sterilization. We didn't even use to sterilized lyophilizers until recently.

Concerning non-sterile products, there are very

few microbiological concerns. Participants said none, but I disagree. For oral dosage forms, transdermal, suppositories, and products that are inherently antimicrobial, they felt that these should be streamlined and of reduced review and scrutiny. And certainly non-aqueous products, such as the metered dose inhalers, nasal sprays, dry powder inhalers, were offered as examples of additional low risk category drugs.

There were a lot of requests for guidance concerning manufacturing process-associated changes. These requests asked in particular for information concerning the categories of filing changes and more examples and definitions so that people could feel confident that they were doing what the agency wanted and communicating properly.

The other advantage to having these guidances is, it was felt, that the agency was in need of internal help here, and this might be a side benefit to it because of many complaints from the industry that recommendations were not consistent, either between offices, between centers, and sometimes between the centers and the field.

So, in summary, we have a lot of evaluation to do internally. We need to determine what we can do to best address these concerns, and we do feel that we can accomplish a lot using process based evaluation rather than

drug product based.

Thank you.

DR. BYRN: Questions for Dave.

(No response.)

DR. BYRN: Our next speaker is Eric Duffy again with GMP.

DR. DUFFY: Steve wants me to talk fast. Now, I'm not from New York, but I'm from Boston, so I can probably keep up.

I'm presenting this on behalf of Pat Alcock who is out of the office today.

The GMP breakout sessions were really central, I think, to most people's consideration of this whole initiative, where the capability of the manufacturer really was a recurring theme all the way through. There was some discussion initially of what the current system was, and I'll kind of breeze by that, however, simply just to say that there was, to me, surprisingly a consensus that the current system really works quite well. The inspectional paradigms that we have in place for ensuring GMP compliance seem to be working quite well.

But for this particular program, there was some discussion about whether or not there should be some what was termed GMP-plus system established where there's something a little bit further than what the current system

was. A number of different suggestions came up with respect to how one evaluates the firm's capability for adherence to GMPs and to have quality systems in place to ensure consistent quality manufacturing.

What are the measures of these? How would the agency assess the capability of this firm to demonstrate exemplary adherence to GMPs?

Some of these suggestions were recall history, for example. It could be an assessment of the body of PAI inspections that had been conducted, review of 483 comments, the recurrence of particular issues. Basically what is the regulatory status, inspectional status of a firm? So, I think what we need to do is try to develop a paradigm to assess the history and a means of demonstrating the capability of a particular manufacturer.

There were other issues that could certainly be measures which might concern whether a firm had been under any consent decrees. Would then some sort of probationary period need to be established to provide the firm an opportunity to demonstrate good manufacturing practices and adherence to GMPs? That might need to be defined?

There was another consideration of the implication this might have with respect to the mutual recognition agreements that we're currently engaged in negotiating with the Europeans, and I think in the future

with Japan, that this may have some impact on that. And we certainly need to take all that into consideration.

Further concerns were that if we were to create this GMP-plus system, that it might create a different set of GMP standards for the drugs on the list versus those that are not. This approach may have a differential impact upon large firms versus small firms, new firms versus experienced firms. So, a fairness issue essentially was expressed.

How one would handle situations where there are multiple companies involved in a supply chain. What clearly comes to mind is drug substance manufacturing where one might have three or four firms involved in manufacturing various stages of a synthesis? Manufacturing intermediates, how would we handle that? Certainly an important thing to consider.

Also, how one would handle changes in ownership or management. Would that have an impact upon our consideration of the reliability and capability of the particular manufacturer?

I think I hit two minutes. There we are.

DR. BYRN: Questions for Eric?

DR. LACHMAN: Eric, you're now discussing a lot of GMP and administrative issues that are ongoing right now within the agency's activities on inspections. So, there's

nothing really novel here. I still think we're getting away from the inherent characteristics of the drug and dosage form and controls necessary to assure reproducibility.

DR. DUFFY: It's a totality of approach in this case, Leon. We're not really divorcing the attributes of the drug itself from manufacturing capability. It's going to have to be interwoven in some fashion.

DR. LACHMAN: Right now there's an intensive, proactive regulatory environment out there from a compliance point of view, GMPs, and so on. They consider all these elements on inspections and what to do next to the firm and so on. So, that's really nothing new that you addressed. And these additional GMPs that you can apply are being applied if you're out there in the field. So, I think we still have to get back to the basic science of the drug and dosage forms and the reproducibility of the controls for the products and active ingredient.

DR. DUFFY: We don't disagree with that at all.

DR. LACHMAN: I think we're muddying the waters a little bit here with bringing in all these GMP issues because they exist now.

DR. DUFFY: Well, we were simply trying to express what many of the participants at the workshop expressed, and that is that we need to have some way of

measuring the capability and qualifications of a particular firm to enter into this program for reduced regulatory scrutiny. If they have a demonstrated history of a capability to adhere to GMPs, to manufacture in a consistent manner, and produce a quality product in a predictable fashion, well, then that's a plus for them for involvement in the program.

DR. LACHMAN: I think the FDA has that now. They have quality profiles of firms based on their inspectional history.

DR. DUFFY: Right, and some firms are turned down for approvals.

DR. LACHMAN: That's right. That's what I'm saying. So, that's nothing I think that we don't have already. That's all I'm saying.

DR. DUFFY: Were there any other questions? Comments? Judy?

DR. BOEHLERT: Just a comment. While I agree with everything that Leon said, I just wanted to add a comment on this concept of up-to-date and meaningful specifications. I don't think industry realizes what kind of task that may be for them, particularly on old products that are compendial. They're following compendial methods. There are no physical tests in the compendia to begin with. So, that's something that needs to be addressed. Those

will probably result in submissions to update old methods, old tests, new impurities that they've now found that have always been there but they didn't see them before.

DR. DUFFY: Those concerns were amply expressed at the workshop.

DR. BOEHLERT: Yes, I'm sure. And it's a lot more work than I think industry is realizing. On a new product that has good controls, perhaps not, but on old products.

I don't know how everybody gets up to the same standard in that case because the methods aren't published in USP. The physical tests, the process impurities. They don't list those.

DR. LACHMAN: I think we need to look at some of the history here for existing products that have been on the market a long time and they've been safe. They haven't caused any health hazards. As the methodology and analytical techniques become more sophisticated, we're going to find more impurities in the products that have been on the market. That's something that we have to consider in addition and not part of this mechanism, I don't think, because those exist now for existing products.

DR. DUFFY: Those concerns were expressed repeatedly.

DR. BOEHLERT: I think if impurities have

always been there, that's a different situation than creating a new impurity because they could, indeed, be qualified for use.

DR. DUFFY: It's just that you now see it.

DR. LACHMAN: That's right.

DR. DUFFY: Shall we move on? Any further questions? Gary, you had something?

DR. HOLLENBECK: Just a similar comment. I think that the essence of this presentation shows that maybe you don't have tier 1, tier 2, and tier 3. These things are so interwoven that they almost have to be considered simultaneously. I'm a strong advocate for rewarding a company that has a history of good GMP compliance, and I think that's a critical part of the whole process.

DR. BYRN: Dr. Chiu? We're going to go to the next steps, and then if people can be looking at these two questions. I think we've discussed many of these issues already.

DR. CHIU: As you can see, we were a little bit disappointed with the outcome of this workshop because we went in seeking scientific input. What we received were a lot more questions, and also the consensus is not the way we think we can readily handle.

However, I do believe -- and I think our

working group also believes -- there is a way to establish criteria, attributes to characterize safe, so-called low risk drugs. Actually the terminology was discussed in the workshop. Many people felt it has a bad connotation because if a drug is on the low risk list, they feel other drugs become high risk. They would like us to think about changing the terminology. So, internally we have discussed maybe we could call it predictable drugs, established drugs, robust drugs. Some people suggest low impact drugs. So, if you care to discuss, maybe you can come up with a better term than low risk.

But everybody understands what low risk means, that from the quality point of view, the product is really prone to defects and they are with those more physicochemical characteristics. Therefore, not much will happen to them regardless how you handle it.

Based on the discussion you had the last time and today and also the workshop and the internal discussion, we thought we need to modify our program a little bit. A lot of people told us internally and externally when I see a drug, I work on a drug, and I review the drug, I know it is low risk. When I see one, I will know it. But if you ask me to define the characteristics in a broad sense, it's very hard.

So, we thought then maybe we should take a

parallel approach. In addition to considering stability 5 years, stable at the room temperature, it has no polymorphism, et cetera, maybe in the meantime, we can also solicit from people what drugs through their experience they think are low risk. Then we can evaluate the characteristic of those drugs and then come up with objective, scientific criteria. So, if we do those things parallel, maybe you can reach there faster.

So, we're going to form subgroups under our current working group to separately address drug substance, drug product, and microbiology issues.

We also formed a group to address GMP. But as Leon said, GMP is GMP. Everyone has to be in compliance, otherwise you already get in trouble.

So, the other input we had from the workshop is, as I said, this is really the concern of so-called high risk manufacturers. The manufacturers will now know what they're doing. Therefore, regardless if the drug is low risk or high risk, the drug made by such a company would become high risk.

So, therefore, the feeling is it is important that you tie in the GMP status not only with the historical status, but also with the GMP status of a specific product on the list. So, if we do that, then that company, to be eligible for this program, must already have experience in

making that particular drug. If we move from that direction, that means the original ANDA must contain full information because the company would not be eligible for this program because they have not made that product yet. So, if we move in that direction, there will be no TANDA, no truncated ANDA.

Therefore, this comes to the two questions we pose to the committee to discuss. The first question is really whether we should take the parallel approach, we should seek input from people from industry, from our reviewers to find the drugs through their experience that are considered to be low risk. Then we use those drugs and analyze the characteristics and see whether from there we could establish a set of objective attributes and acceptance criteria.

The second question is whether we should tie the GMP status to a specific product. And if the answer is yes, we will not for the moment entertain TANDA, and the program temporarily will exclude truncated ANDA submissions.

DR. BYRN: Let's spend a couple moments on each of these. On the first question, any comments from the committee as it reads here, is the approach of establishing attributes and acceptance criteria for drug substance, drug product and microbiology based on the characteristics of

potential candidates of low risk drugs appropriate? Is that approach appropriate? Any comments?

DR. HOLLENBECK: I think the list is inevitable. It is something that's necessary.

But your comments about the process I think are really good. It's like my view of art. I don't know what it is, but I know it when I see it. Here, I think you would be better served to do kind of a retrospective rather than prospective approach. If we sit down and try to identify everything that might be on the list, it's almost impossible to make the list small enough or have any drug ever qualify as being low risk.

However, if you do go through this exercise, I think what you usually find is there's one thing that kicks things off the low risk list, and if you do that for a series of compounds, you'll begin to compile this set of criteria.

DR. DUFFY: We're doing precisely what you're suggesting, Gary. We're kind of delving back and doing a little data mining, one might refer to it as, to really see. We have a product that appears to be robust and perform in a consistent fashion. What is it that makes it do that? We are doing it.

DR. BYRN: I agree. I think you have to do it almost compound by compound early on anyway.

Other comments on number one?

DR. MARVIN MEYER: Is the question whether one should have a subgroup that looks at the chemical and a subgroup that looks at the dosage form, or will they be studied simultaneously by a group? For example, hydrochlorothiazide immediate release tablet versus some type of a controlled release dosage form? If you want to get this thing off dead center, if you took a product that everyone says, well, it doesn't matter what the dose is, it's effective, it's safe, it's stable, it's blah, blah, blah, that's our poster boy, if you will, for a low risk drug, and then kind of build around that and come up with a list and then float the balloon and see how it flies.

Or is the question saying should the agency even be concerned about reducing the regulatory burden based on these attributes.

DR. CHIU: No. The question is the former, not the latter.

DR. MARVIN MEYER: The approach.

DR. CHIU: Yes, it's the approach because even though we formed subgroups, if we identify lists of already the candidates, we will have the subgroup to go back to our files to look at the characteristics of the drug substance of that product, and the characteristics of that drug product as a drug product subgroup. Then we will talk to

each other and then put the things together. So, the reason we want to form separate subgroups is then we can become more focused.

DR. BYRN: Is there general consensus that the response to question number 1 is affirmative, it's a good idea? Okay. I don't think we need a vote on this one.

Question number 2. In effect, this would eliminate the TANDA mechanism right now. Basically what's being said now is that the CGMP status and also its history of that specific product would go into consideration. Are there thoughts on that?

DR. SHARGEL: As a member representing the generic industry, I was, of course, compelled to address this issue. I think the history of GMP certainly is suitable and for new products that generics make or new generic drug products, there are already in place pre-approval inspection and validation batches and other approaches. So, I would like to keep it broader, not specific to a history of GMP.

DR. LACHMAN: I would say that the GMPs apply across the board. They're not geared for any single product. Even on pre-approval inspections, you do a vertical review of the documentation and records to support that product, but you also go broader because your environmental system or your water system doesn't just

apply to a product. You got to look at the totality of the GMPs and the training program. So, you can't just isolate GMPs in a vertical manner. It has to be horizontal.

The quality systems are broad. It's not only for one product. If you're making tablets, you've got to have a quality system for tablets. You make injectables, you got quality systems for injectables. They're not exactly the same as tablets. So, you got to look at the system and not an isolated element.

DR. CHIU: So, you do not think the manufacturing history or experience for a specific product is important related to GMP.

DR. LACHMAN: No, because I think it's all broader than just a specific related to a single product.

DR. BYRN: Where I think some of the problem may come in is in the drug substance side. I don't know, but that's where know-how and so on may play a bigger role in many cases. I guess if you started talking about extended release products and so on, it may play a role in drug product. But certainly to me I would like to see somebody have made some drug substance and see what their record is on making that prior to. So, I don't know whether there's a way to do it with drug substance and not with drug product.

DR. CHIU: Well, I think there is. Maybe we

could split this question into two: 1a means whether GMP status to a specific drug substance is important; the second one is whether GMP status to a drug product is important. Then if the committee can vote on both subquestions.

DR. BYRN: Well, I'm just saying that the manufacturing history might be more important for a drug substance than a drug product.

DR. CHIU: Yes. I mean manufacturing history for a specific drug substance. That's the GMP part.

DR. BYRN: You know, that wouldn't preclude a generic firm from buying it from a well-known manufacturer. This is more like a new manufacturer.

DR. CHIU: Right, a new supplier.

DR. LACHMAN: The API firm supplying an innovator company or a generic company also undergoes inspection by the FDA, and their process is evaluated with regards to repeatability. In certain cases, both innovator companies and generic companies don't manufacture their own API or they manufacture part of their API and farm out part of it. So, your drug master file becomes an important part in the evaluation of this low risk to high risk. I think that needs to be taken into account, the controls like we have for dosage form. What are the controls for the active pharmaceutical ingredient? I think, Steve, that's an

important piece.

DR. CHIU: Can the committee vote on these questions? Because it's important for us to establish the scope of this project.

DR. BYRN: I'm not sure what your question is.

DR. CHIU: The question is whether we should eliminate TANDA, if we could put into two parts the TANDA for drug substance and TANDA for dosage forms.

DR. BYRN: Yes. We need to try to reach a consensus because we are going to have to start at 1:45 again.

DR. LACHMAN: I think there can only be one TANDA. I don't think you can break it --

DR. BYRN: TANDA would just be a drug product. An ANDA would be a drug product. It would be the DMF --

DR. CHIU: I understand. DMF supports the TANDA, so DMF is part of TANDA.

DR. LACHMAN: So, the TANDA would be affected if the DMF wasn't any good. I mean, if the bulk drug supplier wasn't any good, you won't get approval of the application.

DR. CHIU: I understand. Maybe let me explain. The ANDA contains a drug substance part and a drug product part. A drug substance could be supported by a DMF. So, TANDA means truncated ANDA. We couldn't have a truncated

ANDA, both truncated in drug substance information and drug product information. So, if we say the drug substance part of the information is essential for TANDA, then the truncated submission would not apply to the drug substance part.

So, therefore, if I can have a reading from the committee whether the drug substance information should be fully submitted in a TANDA. That's the first question.

DR. LACHMAN: I think it's an integral part of the TANDA. You can't get a TANDA without an active ingredient.

DR. CHIU: Sure, but it will be reduced information. It's not eliminated. Under TANDA, there will be reduced information to be submitted for a drug substance and for a drug product.

DR. LACHMAN: All right, so that has to be still determined.

DR. CHIU: To be determined, yes. We will eventually write a guidance, what would be adequate information for an annual report, and then we thought we could start with the summary, CTD summary of the quality section. That type of information, if it's sufficient for an annual report, it will be sufficient for a TANDA.

So, if you tell me the drug substance cannot be truncated, then we will say the annual report will also be

required to have the full drug substance information and the TANDA will have full drug substance information, only reduce the information on the drug product part.

DR. BYRN: Is it possible just to make a list of drugs from the safest to the less safe and just draw a line somewhere and say these are so safe that it doesn't make any difference who makes them?

DR. CHIU: That's the objective.

DR. LACHMAN: Well, I'll tell you, I wouldn't go that far, Steve, because I wouldn't want to have metal in the active ingredient --

DR. BYRN: Yes, well, we're assuming that they pass compendial specs.

DR. CHIU: Compendial specs are not adequate for all products.

DR. BYRN: I think we have to stop now. I know we haven't gotten a full conclusion yet, but I think we should stop. I think the agency could come back to the committee with more detailed proposals, but continue along both of these lines, and from what the committee said, not kill TANDA. Do not kill a TANDA, but consider our comments and continue.

DR. CHIU: That's fine. We will come back if we have more specific questions. Thank you.

DR. BYRN: That's what I think we should do.

We're going to meet back here at 1:45.

(Whereupon, at 1:10 p.m., the committee was recessed, to reconvene at 1:45 p.m., this same day.)

AFTERNOON SESSION

(1:57 p.m.)

DR. BYRN: Welcome to our afternoon session. This is the open public hearing part. We have had no requests from the audience that's attending to make a presentation, but we do have four five-minute presentations from the Inhalation Technology Focus Group.

The first speaker will be David Radspinner, Ph.D., who's going to give us an update on ITFG/IPAC-RS DCU Working Group progress. He'll explain all this.

(Laughter.)

DR. RADSPINNER: It's only fitting to have more acronyms, isn't it?

DR. BYRN: That's fine. We're used to that.

DR. RADSPINNER: As mentioned, my name is David Radspinner. I'm a member of the IPAC, which stands for the International Pharmaceutical Aerosol Consortium on Regulation and Science. This is an industry association. We formed a collaboration with the Inhalation Technology Focus Group which is a subgroup of the American Association of Pharmaceutical Scientists.

Together what we have done is last year we formed a collaboration to look at CMC issues and also BA/BE issues related to the FDA draft guidance. These technical teams have actually presented some of their concerns at

this meeting back in November. What we'd like to do today is give you an update as to some of our activities.

As you see here, we've been working quite diligently on proposals around issues of CMC with relation to the draft guidance. Also, the BA/BE technical team has been looking at dose-response studies.

With regards to CMC, there are four critical issues we look at, that is, dose content uniformity, particle size distribution, tests and methods, and leachables and extractables. What I'd like to do is briefly update you on dose content uniformity, and then I'll hand it over to Dr. Evans.

Back in 2000, we collected and analyzed the dose content uniformity database and submitted the findings to the FDA. This was back in July. The reference is listed here.

In November, there was a meeting and we reported at that meeting that 68 percent of the products that were analyzed did not comply with one aspect of the dose content uniformity criteria within the draft guidance.

We also met with the FDA back in November, and we met once again in May 2001 to discuss the findings and plans for future work.

What we've done is we've kind of moved on from the review of the database itself, and we've worked very

hard on developing an improved dose content uniformity test, and that's what I'd like to focus on here.

The foundation of this test is originally based on some ideas coming from Dr. Walter Hauck, which I'm sure most of you know, and it's based on a parametric tolerance interval approach. The test design is also similar to some concepts that were developed and discussed within ICH with regard to content uniformity.

We've looked at quality standards implied within the guidance, and it's sort of an approach where we've taken the draft guidance and sort of reversed engineered a definition of a quality statement.

We've also looked at the capabilities within the industry of modern inhalation technology and considered it while developing this test.

The parametric tolerance interval approach, when we compared it to the current guidance -- the advantages are increased efficiency in using the sample information. So, we're not really collecting different sample data, but we're using the information much more efficiently we believe.

By doing a parametric tolerance interval test, we're also improving the consumer protection -- this is in a statistical sense -- while at the same time improving producer protection. So, we're trying to avoid those

batches that fall in the middle.

What's important is we have an explicit quality definition, which is a proportion of doses within a batch that fall within a given target interval.

The acceptance criteria is based on a sample mean, a standard deviation, and what's called an acceptance value, which actually combines the two.

It's a consistent quality standard, but we offer a flexible testing schedule to the producer.

There's also a single test for both within-unit and between-unit variability, and this has been achieved through a parametric tolerance interval test. One of the aspects of that has also been an increased average sample size for testing within the industry.

Where do we go from here? There's a draft report currently under review within the IPAC-RS consortium. We anticipate submitting this in the fall of this year. We also anticipate having a meeting following that with the FDA to discuss this, and we do recommend that this become part of the draft guidance.

I guess I take questions either now, or if you'd like to move through all four presentations before taking questions.

DR. BYRN: I think we will go through all four and then take questions together.

DR. RADSPINNER: Thank you.

DR. EVANS: Good afternoon. My name is Carole Evans, and I'll be presenting on behalf of two of the teams today, the particle size distribution team and the test and methods team.

The particle size distribution team have addressed two concerns on the draft guidance, firstly, the concern that there is a requirement for mass balance within the particle size testing be established as a drug product specification. In this case, the mass balance actually attempts to measure emitted dose, which is appropriately controlled by separate specifications and test methods. However, we agree that this mass balance measurement could be appropriate as part of a system suitability control, but it should not be a product specification. Furthermore, if we're to use mass balance as a system suitability, the limits should be determined during validation studies and not set arbitrarily in a guidance.

Additionally, one of the concerns is that the label claim may not necessarily be reflected by the mass of drug collected on all stages and accessories. For example, there are some products for which label claim is defined by the pre-metered dose rather than the emitted dose, and in these cases, there would not be a match there.

Finally, we've also reviewed some data that

we've collected from a number of products and have found that, in general, the majority of products do not meet this requirement. To date we have collected a large database of data from 35 products and found that only 11 percent of the products -- that's 4 of them -- will actually meet this criteria. We've submitted this initial assessment of the database to the FDA in a paper last August.

As a next step, we'd like to meet with the agency and try and determine the actual purpose of this requirement to try and understand better what the objective of the agency with this requirement is and work with them towards finding an alternate method of addressing their concerns. To this end, we've submitted a proposal to PQRI to have further discussions on the subject.

The second area that the particle size distribution team is working to address is for the use of particle size distribution profiles in bioequivalence testing. The draft guidance proposes a chi-square differences approach to comparing the profiles with test and reference products. The concern is that the chi-square method was developed for one particular product and we're using one particular type of equipment, and the applicability to other products and other test methodologies may be limited and hasn't been demonstrated. Furthermore, the equivalence criteria have been set

somewhat arbitrarily.

The team are currently pursuing an investigation of alternate approaches. Amongst those are the approaches based on bootstrapping of data. Their objective here is to try and find other approaches which may be more discriminatory, would have wider applicability, and would provide a consistent approach for comparisons of profiles. They've submitted a proposal to PQRI to have some work pursued to look at alternate approaches and to look at what metrics for comparisons of profiles may actually have some clinical relevance to help us evaluate bioequivalence.

I'll move on to the test and methods team. The test and methods team has been reviewing the test methods proposed in the guidance, and our objective has been to select methodologies that would be based on development data providing meaningful information about product quality. Our concerns are that some of the tests proposed in the guidance offer little added assurance as to product quality and in some cases may be redundant.

We've collected data on a number of the tests and have developed a database consensus and recommendations to the FDA. We submitted a paper to the FDA in May of this year which proposes alternate language for a number of tests for MDIs. Again, our objective here is to maximize

the value of the controls and tests and minimize the redundant testing.

I will not read all eight. We submitted comments on the tests listed here. Our paper provides a critical assessment of the value of these tests and the development data that may be used to support new product control. We've concluded that a fixed list of tests may not be appropriate as guidance and that the guidance should stress the importance of defining the tests used for a product during the development process, and that we should eliminate those controls which we feel are redundant. We're at the moment working on developing proposals to put forward to PQRI.

Thank you.

DR. BYRN: The next speaker is James Blanchard who is going to address leachables and extractables.

DR. BLANCHARD: Thank you and good afternoon.

I'd like to update you on the work of leachables/extractables team.

We have reviewed both guidances very carefully, basically trying to look at them from a user's perspective. From an implementation perspective, we feel that we can more effectively implement the guidances if we have some thresholds to work with which we can agree upon and the agency can agree upon as well. So, one of our concerns is

proposing or trying to propose adequate, appropriate thresholds for reporting, identifying, and qualifying leachables and extractables.

Also, we have found some terms that are very important that are a bit unclear in terms of how to interpret them. So, we are also looking for clarity to define concepts such as correlation, particularly how a leachable will be correlated with an extractable because that's actually a very important in implementing the guidelines and further testing.

Also, there is a term called "critical component." What exactly is a critical component? What has to be actually done to test a critical component? So, we'd also like some more clarity on that definition as well.

So, what we've done to start this process is that we've started gathering data from the industry and the one set of data we did collect was for leachable and extractable data on specific drugs to see if correlations did exist between these leachables and extractables for this.

We've also collected other types of data. We've also formed a toxicology working group of expert toxicologists from industry to look at the qualification issues, and together we have put together a report which

we've now submitted in March.

So, I'd like to go through some of the highlights of some of the areas in each of the guidances that we think would help for clarity or some help with the agency.

First of all is the definition of a critical component. We're proposing that a critical component would be any part of the device that would be in direct contact with either the formulation, the patient's mouth or mucosa. That would be what we would be testing going forward in our characterization of the extractables and the leachables.

Next, getting to the idea of thresholds, we are proposing a reporting threshold of 1 microgram per gram in the controlled extraction studies of the raw materials. At this level, we are thinking that you won't get complete structures, but maybe you can an idea of at least the class of the compound you're dealing with. Then when you have 100 micrograms per gram, we would set that as the identification threshold where we would have confirmed structures.

Now, moving ahead to leachables, basically these are when you're really working with the dosage form and the excipients. The guideline right now calls for doing toxicological qualification on extractables, and we really want to make a strong case to only do the tox

evaluation on leachables.

Secondly, getting back to the point of correlation between extractables and leachables, we would like to say a correlation exists between those two when you can qualitatively, either directly or indirectly, relate a leachable to an extractable.

Third, again getting back to the concept of the threshold, we are proposing a reporting threshold of .2 micrograms total daily intake, TDI, as a reporting threshold and a 2 microgram TDI for identification threshold for each leachable.

Then lastly, in the routine extraction studies, which we would be doing to maintain or to make sure that we have adequate control over the components coming in, we would like clarity in terms of what is the actual purpose of these studies. We are proposing that these should be used to ensure that the extractable profiles of components used in commercial manufacture remain consistent with profiles and components used in the pivotal development studies, and they are not a substitute for in-process control or supplier qualification.

So, we've put together two flow charts to help capture some of these issues. Also, the second flow chart will give us more detail on the tox qualification, which I haven't got into yet.

But we're starting off. This is taking us down through the routine extraction, controlled extraction studies, and into leachable studies. The first box here is starting off with the critical component, again a component in direct contact with the formulation, the patient's mouth or the nasal mucosa. And we're saying that if that's true, yes, then you do a controlled extraction study where we would do qualitative and quantitative assessment of all peaks greater than 1 to 20 micrograms per gram.

And then going down to the next blocks, we would then go on an do a leachable study on this material, and we would do that using aged registration batches through end of shelf life to quantify in drug product the extractables identified above. And in this process, we would quantify all peaks greater than .2 micrograms TDI. And we would provide identity and quantity of all leachables to the toxicologists for assessment, which is the next box.

Just going over, if the critical component did not contact the formulation or patient's mouth or mucosa, then we go over to the no box. Then we can do other testing that would be sufficient such as identity, dimensional properties, and so forth.

Going forward on to our routine extract studies, then we would be doing that and other testing if

necessary. So, we have it all boxed up.

Now, going on to the qualification thresholds here, we have individual leachables above .2 micrograms TDI and if we are saying that's true, then we go down a couple of paths. We'll go down the easy route. Greater than 5 micrograms TDI would be our upper threshold. And then we say we confirmed structure, and then we would basically do a full tox assessment of that.

However, if there are greater than .2 micrograms and less than 5 micrograms TDI, we would assess whether there are structural activity concerns, and then we would do a tox assessment or not, depending upon what's happening with that assessment.

If we go up here to the top, if it's no, if the leachables are less than .2 microgram TDI, then we would do no further evaluation.

So, these are the thresholds we're laying out for the qualification.

I'd also like to make the point we are also opening up a category for special compounds which may have SAR concerns or be nitrosamines or PNAs that are known to be a problem. So, we would treat those on a case-by-case basis. These thresholds may or may not apply to them.

So, going forward, we strongly encourage incorporating into the guidances these thresholds for

identification, reporting, and qualification, and we are proposing that we have an ongoing discussion through various fora with toxicologists and chemists to work through these thresholds. We also have submitted our proposal to PQRI.

So, just to sum up what we've talked about here, the ITFG/IPAC-RS collaboration plans to bring several proposals to PQRI and continue discussions with the agency regarding the new DCU proposal.

We hope that through the meetings of the OINDP Subcommittee, Advisory Committee on Pharmaceutical Science, PQRI, and other appropriate fora, the work of the ITFG/IPAC-RS collaboration will be carefully considered.

And we believe that FDA and industry will be better able to respond to the needs of patients by expediting the availability of new OINDP products while maintaining appropriate standards for safety, efficacy, and quality.

We appreciate your consideration. Thank you for your consideration. I'll turn it over to the BA/BE presentation.

DR. BYRN: We're going to go ahead with Dr. Sequeira, and then we will have any questions or comments from the committee after this presentation.

DR. SEQUEIRA: I'll be brief. I'll try to keep

it to under 5 minutes.

I'm a member of the BA/BE team, and this team has been in existence for a year and a half. During that time, we have been very productive and worked constructively on this very difficult issue, and some of our efforts are described on this slide.

We've made four presentations on this topic at meetings like these, and we've also submitted three reports to the FDA on this topic.

We've conducted a review of the current literature on this, a task which has stretched over this the year and a half. We do not have substantive new approaches on dose response, but we feel that risk assessment and risk management must be done first to put this whole issue of nasal drugs into proper perspective, as I'll discuss a little bit later.

The in vitro study designs in draft BA/BE guidances are useful for comparability of products, but unproven in value for establishing clinical equivalence and substitutability.

Based on the data presentations made by the FDA at Tuesday's meeting and this morning, we agree with the OINDP Subcommittee recommendation of selecting one dose between the test and reference in the clinical study and the inclusion of a placebo.

We also agree that the traditional treatment study offers the most appropriate study design for assessing nasal drug products intended for local delivery and concur that the typical 2-week duration of this study is appropriate.

However, there is a need for the draft BA/BE guidance to further develop the statistical requirements for this study, even if it is to be used to confirm the comparability and substitutability of reference and test products. As most of you know, the weakness of this design is its dependence on seasons and the measurable placebo effect.

I'd like to present here a case study that is very relevant to this topic. This is work done by Casale, Azzam, Miller, and others and published in 1999 in the Annals of Allergy, Asthma, and Immunology. It deals with the demonstration of therapeutic equivalence of generic and innovator beclomethasone in SAR. I'd like to point out three issues with this paper.

The first, the authors state that the primary objective was to compare the test product, which in this case was a generic, at two doses versus the placebo. And their secondary objective in the paper was to compare the test versus the reference innovator product. We clearly think that a reversed hierarchy is more appropriate here

and that the secondary objective should have been the primary objective.

Secondly, the study was designed as a different study, not really as an equivalence study. The sample size was adequate to distinguish between active and placebo, but inadequate to distinguish between the two types of BDP, had there been a difference. This is a typical common design error. Failure to differentiate between the two products dose not mean that a difference does not exist, had the design been more robust to pick up this difference.

The third issue is the order of administration. The active was followed by a placebo, and the treatments were not randomized. Hence, we have the bias of washoff or washout by the placebo.

We really didn't mean to critique this paper, but only to present it as an example of the need for further work in this area.

Therefore, this leads me to the key steps to confirming the correct study design, which are summarized on this slide. Firstly, the draft guidance must address the issue of substitutability and not confuse this with comparability. Secondly, we need to develop statistical requirements for this study design for comparing the test and reference products. And the team seeks the agency's guidance concerning this issue.

One way to deal with open questions on bioequivalence study design is to use risk management to focus scientific investigation on those critical elements whose uncertainties should be given priority as the development of the guidance progresses.

We've highlighted here three risk areas present with locally acting nasal products in the context of clinical comparability and substitutability. The first is the comparability of the container closure system to assure comparable spray delivery. Here I must add that the FDA has done an excellent job with the guidance they have given for Q1 and Q2, but that takes care of the formulation. What we need is something like I'd like to coin, Q3, to give us some measurable parameters on the packaging of this particular product so we can be assured that the spray is comparable between the test and reference product.

The two other issues concern particle size differences between the test and reference product and the implication of these particle size differences on both the onset of action and a systemic exposure of the product.

As Dr. Adams very well knows, people use different micronizers throughout the industry and end up with different particle size distribution products for the drug substance. People also know that you can essentially nanosize the drug product using microfluidization

techniques and achieve drug product with very fine particle size. And people also know that you can make a mistake and do a lousy job on micronization. So, you end up with particle size being a very critical issue here.

And it cannot be presumed that an in vitro test that correctly correlates with the local actions will also be predictive of the systemic outcome.

My last slide is missing, but I'll read it out to you. The container closure system and particle size are two key risk areas that remain to be addressed regarding clinical comparability and substitutability. We agree with the agency and the OINDP Subcommittee that particle size is important in determining standards for orally inhaled nasal drug products. We agree that Dr. Adams and the FDA have rightful concerns on drug particle size in the emitted spray as being one of the most critical parameters that could affect local efficacy and safety. In fact, their sister division on the pulmonary side considers dose delivery and particle size distribution of that dose to be a very critical element for these products, even if they are line extensions of new products.

So, after giving you all those thank you's, I would like to now throw out a challenge, and I'd like to recommend that an efficacy study be developed to investigate the onset of action, via either a park study or

an EEU study, so that we could at least be assured on substitutability of these products because a very important parameter of these products is onset of action. So, in addition to the traditional treatment study, we'd like to suggest a short-term 1- to 3-day study in the park or in the EEU to get a feel for onset of action.

Thank you.

DR. BYRN: Thank you very much.

Are there questions from the committee for any of these speakers? Judy? For Dr. Sequeira.

DR. BOEHLERT: Yes, for Dr. Sequeira. I have a question regarding particle size. It's very easy to control and measure particle size on the active ingredient. That can be done. The techniques are available and you can show comparability very readily.

In your experience, does that particle size change once it's formulated, and are you going to see a difference from one product to another?

DR. SEQUEIRA: Yes, in fact, Dr. Boehlert, Dr. Poochikin gave us a dissertation on the five or six factors that can change the particle size of the drug in the final formulation, because after the drug is compounded by one of many, many techniques where there can be homogenization or they can use other kinds of techniques, there could be changes occurring during compounding, during filling, and

then finally on stability. And he listed a few more factors that I have the time to cover.

DR. BOEHLERT: Is that reducing the particle size or increasing the particle size, or both?

DR. SEQUEIRA: Sorry?

DR. BOEHLERT: Does the particle size go down or up or either?

DR. SEQUEIRA: It could go either way, depending on the manufacturing.

DR. BYRN: Dr. Meyer.

DR. MARVIN MEYER: This wasn't your presentation, but I was curious how the threshold limits were established for the extracteds and items leached.

DR. BLANCHARD: If you wanted, I could give you slides. We have prepared slides to describe this if you want to go through the process, or I can give you just a high level -- very high level?

High level. Basically we worked from the 5 microgram TDI. We compared that to daily exposures a person would get to ambient air pollution. So, basically we're trying to look at what are people exposed to every day and what do we accept as being safe every day.

So, there's actually a study called the Harvard Sick Cities Study that measured air pollution concentrations and related them to mortality and

cardiovascular problems. In that study, they found one city that was actually very, very clean. It was Portage, Wisconsin, and it had a concentration of 18 micrograms per cubic meter of these particles. Actually that's very, very clean air compare to all the other cities in the U.S.

We used that as a reference point, realizing we've got an added safety factor just by being the fact it was very clean air. We calculated what people would be exposed to in that city at different ages and also for people with disease, and said basically these are the different ranges they would be exposed to, then looked at the safety factors we're talking about. So, basically the 5 microgram TDI stands up very well when you do that analysis. We're talking about being 3 percent or 9 percent of what you'd be exposed to due to ambient air pollution in those cities.

We've also done comparisons with being exposed to different MDIs, high dose MDIs, low dose MDIs, acceptable residues from metered dose inhalers. So, we have a four-pronged rationale based upon that.

So, basically the ambient air pollution one is the top one actually in terms of what's driving that.

Do you want to get into the analytical thresholds at all?

DR. MARVIN MEYER: No. I was just curious.

I'm not in a position to debate whether that's good or bad. I just wanted to know how you did it.

DR. DOULL: Steve, let me follow up on that, Dr. Blanchard.

I don't know whether you're aware. Alan Rulis has put together a threshold of regulation for Food and Drug. It has to do with packaging materials. It really is in the food section, but it's a very similar concept.

DR. BLANCHARD: Right.

DR. DOULL: And I was struck by the fact that your TDI is similar really to what Rulis has --

DR. BLANCHARD: Are we talking about the threshold regulation which is a .5 parts per billion?

DR. DOULL: Yes.

DR. BLANCHARD: Right. We're familiar with that. We actually reviewed that, and we were looking to incorporate some of that rationale in our thinking. So, we are aware of that.

DR. DOULL: His argument is that no matter what the agent is, even if you take the carcinogens, whatever list of carcinogens that go with that rationale, that is in fact a threshold of concern that is reasonable.

DR. BLANCHARD: And the rationale there was that even if it was unknown to be carcinogenic today, if it was later found to be carcinogenic, it was still be so low

to be trivial.

DR. DOULL: I had one other question. You talked in there about using SAR, structure activity.

DR. BLANCHARD: Yes.

DR. DOULL: Are you talking about components of the molecule or are you talking about the molecule itself? You're saying if it's cleared by SAR, then --

DR. BLANCHARD: With SAR, you're looking at components where basically you find a functionality that would be of concern. Then that would raise a red flag for you. We could work this through with the agency, but you could take a conservative approach and say, well, if we know this is problematic in functionality, then we would put that into a special category and give it further analysis.

DR. DOULL: You mentioned nitrosamines, for example. You could say all those agents that are similar you're going to put them in the same bag and be concerned about them.

DR. BLANCHARD: Right.

DR. DOULL: Or you could be looking for quaternary ammonia or something which should be a part of the thing.

DR. BLANCHARD: So, I'm thinking we're going to look at functionality groups, not the whole compound.

Both. The nice thing about nitrosamines is that you know going in that these are well characterized compounds. You know you should be looking for them and you are expected to be looking for them.

DR. DOULL: It's kind of a decision tree.

DR. BLANCHARD: Right, and we can handle it on a case-by-case basis.

DR. DOULL: Well, that's interesting.

DR. BYRN: Thank you very much. We'll be sure to provide this information to the people who are writing these guidances, and I'm sure they will take it into consideration.

Now we're going to go on with the next session, and let me introduce Dr. Lachman and Hollenbeck who are our guests for this session also. Both of them have spoken before and are on the left.

First, Dr. Ajaz Hussain is going to give an introduction. Dr. Hussain is acting Deputy Director in OPS.

DR. HUSSAIN: Good afternoon.

The afternoon session is actually taking a look at some future directions. I will not ask you to vote on any of these, but I think we would like comments, recommendations on what your thoughts are on the two topics that we present to you this afternoon and start to take a

look at some of the new directions and bringing new science and technology into manufacturing.

The topic I have chosen is optimal application of in-line or at-line manufacturing controls in pharmaceutical product development. For the last couple of years, our labs within FDA -- actually more than a couple of years -- have been working with some of the new analytical methods which offer, we think, significant opportunity. A number of publications that I provided to you in your handout material were to illustrate the type of applications that are feasible, and other chemical industries -- indeed, in fact, food industries -- have adopted some of these and are benefitting from these technologies. Pharmaceuticals have not done so and I feel that's an opportunity that we can have significant public health and economic benefits if we can have optimal application of modern in-line and at-line process controls and tests in pharmaceutical manufacturing.

One could look at that as a hypothesis, and that's what I'm presenting to you. The goal here is to initiate public discussion on opportunities and challenges associated with regulatory application of what we call process analytical chemistry tools in the pharmaceutical industry.

I have invited Dr. Raju from the MIT Sloan

School of Management and Chemical Engineering Program which is focusing on pharmaceutical manufacturing to discuss with you anticipated win-win opportunities. The MIT program is in conjunction with a number of companies that has looked at modern manufacturing methods. I hope you get not only the time and cost saving type of information from him, but a sense of what engineering applications to pharmaceutical productions can do for us.

As an introduction of what I mean by process analytical chemistry, here are the many different technologies that are part of process analytical chemistry, and the goal here is to have real-time characterization analysis of samples or material and to have those decisions as close to the processing step as feasible. Generally these are accomplished without sampling and are multivariate in their nature.

Two very common examples are near infrared and Raman spectroscopy in the transmission mode, as well as the reflectance mode. These essentially can be within the processing unit itself or would be close to the processing unit, so that you don't have to collect a sample, and information about the sample is gathered at the site, and decisions could be made rather quickly, as opposed to the conventional method where you collect the sample, do the analysis, wet chemistry, and so forth. So, you're looking